

EGBERT (S.)

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BY

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WHEN Professor Koch first announced the discovery of the tubercle-bacillus, and showed that it was probably the exciting cause of all cases of tuberculosis, many members of the profession felt, and all hoped, that a means both of preventing and of curing this hitherto very intractable malady would soon be forthcoming; and when, later, after bacteriology had attained the dignity of a science, and the germ-theory was generally accepted, Dr. Samuel G. Dixon published the results of his work with devitalized tuberculous matter upon animals, and Koch announced some time afterward similar results upon the human system from his work with so called tuberculin, the belief was widespread that we were on the verge of the solution of the problem. But when further trials of this new agent failed to sustain the promise of the earlier reports concerning it, the rebound of professional opinion carried us backward and probably beyond the point at which it should rest at the present time.

As for myself, I still have abundant faith that we shall ultimately be able to protect and aid humanity to a greater degree than we do now; for not only



is this faith strengthened by my experience and work with Professor Dixon, both before and at the time when he first announced that he had been able to render certain animals immune to tuberculosis, but also because both the progress of science and the logic of events seem to be pointing the way in which such immunity will be eventually secured. Accordingly, I have ventured in the present article to sketch what seems to me to be a logical and scientific course by which a practical method of securing immunity from tuberculosis may be discovered, doing this not so much in a spirit of prophecy as to show that we shall probably still have to employ to the utmost all those hygienic measures that we now know to be of the greatest value in the prevention and cure of tuberculous troubles.

It will be well to note that tuberculosis, whether of pulmonary or other tissues, is a disease essentially different in a number of respects from the majority of other affections due to pathogenic organisms. It is chronic rather than acute; it destroys by slowly undermining and sapping the body's strength rather than by quickly overwhelming the vital activities with toxic bacterial products; it is not self-limited or limiting, and it especially requires a predisposing diathesis or condition of the tissues. By this last statement I do not wish to intimate that other germ-diseases are not favored by an unhealthy or abnormal state of the system, or that the rapid inoculation of large numbers of tubercle-bacilli might not produce the disease in a hitherto healthy subject; but mainly to emphasize the fact that though all dwellers

in communities must be more or less liable to the reception of these specific germs, only those that have a peculiar condition of the system, whether congenital or acquired, are especially prone to the disease. For example, Bollinger has shown that one cubic centimeter of sputum from a tuberculous patient may contain from 800,000 to 960,000 tubercle-bacilli, and that the average patient throws off from 30,000,000 to 40,000,000 of such germs per day; Dr. Prudden, of New York, has computed the number daily from a single patient as over 20,000,000; and Dr. Nuttall, of Johns Hopkins University, has demonstrated that in certain cases they may reach the enormous number of 4,000,000,000 per diem. When we consider how few, comparatively, are the tuberculous patients that take pains to destroy or disinfect their sputum, it is not hard to believe that these parasites are present in considerable numbers in our environment, even though we grant that a large percentage of those expectorated immediately experience conditions hostile to their future growth or existence. Cornet and many others have shown that the bacilli are practically always present in the dust from apartments of tuberculous patients; many gynecologists believe that the increase in cases of tuberculosis of the female organs is due to the prevalence of the germs in street-dust; and Professor Dixon and myself have observed them in considerable numbers in samples of dust from certain of our Philadelphia street-cars.

Can we doubt, then, that each one of us takes into his economy at one time or another, either

from the air, drink, or food, sufficient of the germs to cause the disease, were he only in the condition necessary to its inauguration?

Moreover, the study of the malady itself seems to indicate that its progression is due not so much to the ravages of the hostile parasites as to the vital weakness of the tissues that should naturally oppose and destroy them.

Consequently, the questions that naturally arise are: What is this precedent condition of the body that is usually necessary for the incurrence of the disease? And is not the true protective immunity and cure each to be had by the securing of a change from this tuberculous predisposition to a more normal and healthful condition? Empirically, we know that this latter is just what happens whenever a patient is really cured of tuberculosis.

But what is the abnormal condition? Evidently one of faulty assimilation and abnormal tissue-metabolism. When we study the causes that predispose to pulmonary tuberculosis and other tuberculous diseases we see at once that they are those that favor faulty digestion of food, improper assimilation, deficient oxygenation of the blood, and, dependent upon all of these, the construction of weak, unstable, and unresisting tissues. And though we may seem temporarily to get good results from the use of antiseptics and other drugs, aimed with destructive or retarding intent at the germs themselves, do we not secure permanent benefits only when we employ reconstructives and use measures that will improve the digestion and the oxygenation of the blood, and that will build up new, strong, and healthy tissues instead of weak

and yielding ones? Is it not for this that we carefully watch the diet, prescribe outdoor exercise, and send our patients to other climates?

Dr. T. J. McGillicuddy, in a recent article on "The Dietetic and Hygienic Treatment of Consumption,"¹ says: "To secure healthy, rich blood for the repair of diseased tissues we must have proper food and good digestion." "First, we must prepare the digestive tract and the tissues of the body to receive and assimilate the nutriment, and then we must select the most nutritious food, and so prepare it that it will be readily assimilated. Pulmonary tuberculosis is too often considered to be a local disease and treated as such. We must remember to treat the whole system, which is in a pathologic condition. The diet for the consumptive must be a scientific diet, based on a knowledge of what the different kinds of food do for the organism. This (dietetic) plan of treatment to be effective must be systematically carried out, and both physician and patient must steadfastly avoid that complete dependence on drugs which converts the wisest method of treatment into blind empiricism. There are many factors necessary for the successful treatment of consumption—rest, mental and physical, pure, dry air, gentle exercise in the sunshine—are all important; but these are as nothing if the nutrition does not receive proper attention." Nor should we forget that Pettenkofer and Voit have shown that the absorption of oxygen is determined by the nitrogenous substances comprising the tissues of the

¹ The Dietetic and Hygienic Gazette, November, 1894.

body, and that, as Fothergill says, "the presence of nitrogenized structure, and its participation in the action going on there, is a necessary condition for the manifestation of any vital energy or any chemical change in the body."

I have indicated in but a general way the state of affairs favoring tuberculosis. We are not able as yet to demonstrate exactly the condition of each organ in a person of tuberculous diathesis antecedent to the beginning of the disease itself, but I am inclined to believe that a close study of most cases will show that there are primarily imperfect digestion of proteids, abnormal hepatic action, and certain changes, both of kind and quantity, in the nitrogenous products of metabolism. In other words, the stomach and liver are more often primarily at fault than the lungs, though it may happen in some cases that the derangement of the former organs was at least partially due to faulty respiratory action or habits, bad air, imperfect oxygenation of blood, etc.

Just here I would suggest a hypothesis that appears to me, upon rather thorough investigation and inquiry, to be altogether new. May not the condition of the blood, as expressed by its coagulability, be a measure or index of the kind of tissue, as regards firmness and resisting power, which is constructed from it or by the metabolism of the body? The clotting of the blood and formation of fibrin by the antecedent production of fibrinogen, fibrinoplastin, and, possibly, a third substance, seems, at first sight, to be an extremely elaborate and unnecessarily excessive expenditure of energy on the

part of Nature to provide for emergencies or conditions that are always abnormal, especially as she is prone to act simply rather than complexly, whenever possible. Why may not the principal purpose of the fibrinogen, fibrinoplastin, etc., in the blood be to assist in the construction of the active and supporting tissues of the body rather than to form fibrin solely to repair lesions of the circulatory system?

In addition, we may note that certain substances which increase the coagulability (*i. e.*, the fibrinogen, fibrinoplastin, etc.,) of the blood have been successfully used to produce temporary immunity, at least from tuberculosis and kindred diseases in susceptible animals, and that their analogues or derivatives are to be found in excess in the blood of those who are of a diathesis the opposite of that which we call scrofulous or tuberculous; while, on the other hand, substances known to decrease the blood's coagulability are very likely to be found in the circulation of those whose digestive functions are of the faulty character that predisposes to tuberculosis. For example, Dr. Dixon has shown, in an article to be mentioned later, that the substances employed by himself, Koch, Vaughan, and others, in their experimental work on this subject are all analogous and more or less closely related to the amid group of metabolic products; while we already know that such substances as nuclein, leucin, tyrosin, glycin, etc., increase the coagulability of the blood,¹ and, *per contra*, that albumoses, products of

¹ Waller's Human Physiology, 1893, pp. 19-20.

the imperfect digestion of proteids, decrease and even temporarily destroy the coagulability of the blood,¹ and everyone knows how prone tuberculous patients are to hemorrhages that are difficult to control owing to this lack of coagulability. There also seems to be a very decided relationship between the susceptibility of the various animals, including the healthy human being, and the coagulability of the blood of the respective individuals, though I must admit that there is not so much evidence at hand as I would like to have on this point.

Believing that much more can be adduced in support of the hypothesis suggested, and that it is not altogether a visionary one, I shall hope to be able to discuss it more thoroughly in a future paper. Reverting to our theme, it is essential that we should discover, if possible, the manner in which the tubercle-bacilli inaugurate the disease in a subject predisposed or susceptible to it, and the means or method whereby the predisposition or susceptibility of the whole constitution of that subject may be so altered that the germs may have no power of virulence, growth, or vitality within the system.

As to the former, we know that tuberculosis proper, that is, the formation of miliary tubercles, always begins as a coagulation-necrosis, and as we may consider from the statements and definition of Vaughan that the specific product of the tubercle-bacilli is a nuclein, which latter is one of the class of substances increasing the coagulability of the blood, it is not impossible that the following process

¹ Ibid., p. 23.

occurs in the susceptible subject: A certain number of the bacilli finding lodgment in a certain part of the system, such as one of the alveoli of the lungs, and escaping immediate destruction, owing to the weakness of the body's resisting powers, begin to multiply and to elaborate their special product, at the same time acting as a focus of irritation, and causing a determination of leukocytes to the immediate neighborhood of their nidus. Then, as soon as the toxic product is in sufficient quantity, either acting directly or by inaugurating the reactionary production of a secondary nuclein by the leukocytes, localized and circumscribed coagulation occurs, and the enclosed leukocytes are deprived of nutrition, and are powerless further to oppose the parasites, which, still multiplying, continue the process so familiar to every pathologist. Whether the foregoing picture of the incipency of the tuberculous process is a correct one or not, the consideration of the means for securing immunity does not depend upon it, for the latter has been shown to be based on the antecedent condition of the system rather than on the actual processes of the disease.

The fact that such investigators as Dixon, Koch, Vaughan, and others have been able to secure a condition of immunity in many susceptible animals is proof that we shall ultimately be practically successful with the great mass of human beings. To the objection that some may raise, that the conditions are not the same in the two classes of subjects, I think that, following out the thought suggested in the foregoing coagulability (?) hypothesis, it can

very likely be shown that the difference, whatsoever it may be, is one of degree rather than of kind.

The first thing to be noted is the close relationship existing between the agents employed by all those who have obtained notable results, and of these agents to the nitrogenous products of normal animal metabolism. As Dixon was the first to secure anything like immunity to tuberculosis in animals—I myself having seen him do this almost if not wholly a year before Koch's announcement of his work with tuberculin—so he was the first, I believe, to show that there might be produced from cultures of the tubercle-bacilli a substance strongly resembling certain well-known nitrogenous products of metabolism, and that these latter would give, when injected into both healthy and tuberculous subjects, closely similar results to those obtained by the injection of his protective material and the practically identical tuberculin.¹ More recently Vaughan, who is using the nucleins of yeast-cells and of the spleen in this work with apparent success, has shown that the nuclein-bases yield bodies of the xanthin-group, which latter, in turn, are very closely related to the amid metabolic group of which I have just spoken.

In this connection it will not be out of place for me to call attention to Dr. Dixon's most recent and extremely interesting article on "The Possible Relationship Between the Tubercular Diathesis and

¹ Vide proceedings of the Academy of Natural Sciences, November 18, 1890, and February 21, 1894. Also, the Times and Register, September 26 and October 17, 1891.

Nitrogenous Metabolism," in which he not only considers this relationship much more fully and thoroughly than I could venture to do at this time, but also proposes a line of experimentation which I feel would yield valuable and interesting results if carried out. He has even gone so far as to suggest "that it might possibly be advisable to endeavor to produce a temporary condition of gout or lithemia in our tuberculous subjects, hoping thereby to possibly supply that in which the pathological tissues are deficient or to alter the condition of the tissues either in kind or degree—to change the soil, as it were, so that either the hostile pathogen could no longer find in those tissues a suitable nidus, habitat, or environment, or that the vital activities and resisting agencies of the body would be increased and strengthened sufficiently to overcome the disease-germ before it could multiply and produce its harmful effects in the body." It is also interesting, inasmuch as many now believe the therapeutic efficacy of cod-liver oil to be dependent upon its alkaloids, to note that three of the latter closely resemble urea in structure and formula, and that the other three are closely related to a combination of the glycerin and amidogen radicles.

By this I do not mean to create the impression, any more than does Dr. Dixon, that by the use of the amids results or reactions are to be obtained exactly similar to those due to tuberculin; for the latter, being a specific product of the bacilli, most probably causes a specific action in those cells and tis-

sues that react to it, just as the diphtheria-antitoxin of Behring and Roux is produced only by the influence of the peculiar product of the diphtheric bacilli.

With this evidence, and granting that the opinion expressed in the earlier part of the paper, that in most cases of predisposition there is "primarily imperfect digestion of proteids, abnormal hepatic action, and certain changes of kind and quantity in the nitrogenous products of metabolism," is well founded, it certainly is not difficult to surmise a connection between these various amid substances, all more or less closely related, and the metabolic activities and functions concerned in the production of a predisposing diathesis.

We have as evidence of the manner in which the inoculation of these toxins, nucleins, etc., secures or induces protection the work of Buchner, Nuttall, Vaughan, McClintock, and others, which goes to show that the inoculated substances incite or stimulate the leukocytes, and possibly other active cells of the body, to the elaboration and secretion into the blood-serum of secondary nucleins, antitoxins, alexins—call them what we will—which are not only germicidal but also antagonistic and, as it were, antidotal to the bacterial poisons. This is the principle underlying the new serum-therapy, which is apparently proving itself so successful in the treatment of diphtheria, tetanus, etc., and we may thus the more readily accept the reports of Vique-rat's success in gaining immunity from tuberculosis by the use of the serum of asses, though even in his case it will doubtless be found that, like Dixon and

Koch, he has for his primary agent the toxin or nuclein of the tubercle-bacilli.

From this point we may take one step further, to inquire into the physical nature and structure of the cells secreting the protecting alexin, and then we must wait for light to be shed in the future upon the still hidden processes of the body. Bütschli has arrived at the conclusion that the framework of protoplasm must be "a fluid substance insoluble in water," and that "it must be formed by a body which has arisen from a combination of albuminoid and fatty acid molecules;" while Reinke believes that this so-called *plastin* is a "combination of albumin and *nuclein*, possibly further accompanied by a number of molecules of a fatty acid belonging to the stearic or oleic acid series."¹ The connection between this and what has already been said about protective nucleins (alexins), and also in relation to my hypothesis regarding the constructive functions and processes of the body, must be obvious to everyone.

In the foregoing I have tried to collate and arrange logically the knowledge that we already possess concerning this important question, and though it is difficult to place the facts in their proper order, and the proofs of some of them may not be so positive as we should like them to be, I trust that I have made clear the points in question, viz. : That a predisposing condition is essential to the inception of the disease; that immunity has been produced by a number of investigators in susceptible

¹ Bütschli : Protoplasm and Microscopic Foams.

animals; that the substances thus successfully used are very analogous one to another; that they probably act by stimulating the leukocytes and other active cells of the body to the production and secretion into the blood serum of nucleins or alexins which tend to neutralize the bacterial poisons, and that these agents, favoring immunity, also increase the coagulability of the blood, which being decreased in the tuberculous condition and for other reasons given, may possibly be important as an index of the formative or constructive powers and processes of the system. I also hope the paper may serve to indicate the direction in which we can reasonably look for further advances in this important matter. But, though there is fair promise for future success in the protection of humanity against tuberculosis, we must not forget that whether this be attained through the inoculation of tuberculin, nucleins, serum, amids, or, possibly, other substances that will increase the formative and constructive powers of the blood and tissues, there will always be prime necessity for the additional and assiduous employment of those broad hygienic measures, such as exercise and life in pure air, respiratory gymnastics, freedom from mental worry or fatigue, improvement in gastric and hepatic digestion, etc.; and I do not go too far, perhaps, in saying that without these latter the use of inoculatory methods alone will probably prove illusory and far from satisfactory. In other words, it is the predisposition rather than the attacking pathogen that needs attention, for with the former wanting the latter will be impotent for evil under all ordinary

conditions. By this I would not deprecate the use of protective inoculations in all predisposed or incipient cases as soon as the proper substances and the means of using them shall be surely known ; but simply advise against the error of placing sole reliance upon them to the exclusion of what must always be of paramount importance.

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